more elusive and took much longer to achieve. One early constraint came from the work of Ochoa, who established that up to three molecules of ATP were formed per oxygen atom consumed. This indicated that the reactions forming ATP must occur at multiple steps along the electron transport chain. But what were these reactions? Lippman (1946) proposed that ATP synthesis along the electron transport chain would follow a scheme similar to that already known for glycolysis. He presented it in abstract form as a sequence of two reactions (the formulae above the line) achieving the overall effect of adding a phosphate bond to ADP to yield ATP (the summary formula below the line):

$$\begin{array}{c} AH_2 + B + P_i \rightleftharpoons A \sim P + BH_2 \\ \underline{A \sim P + ADP \rightleftharpoons A + ATP} \\ AH_2 + B + ADP + P_i \rightleftharpoons A + BH_2 + ATP. \end{array}$$

In these formulae, A denotes a substrate which is oxidized in the first reaction coupled with the reduction of another substrate, B. (A and B may be successive cytochromes in the electron transport chain, for example.) As A is oxidized it forms a high-energy bond with phosphate. In the second reaction, ATP is synthesized via the transfer of this bond to ATP.

This scheme was elaborated when it was discovered that the first of the two ATP-producing steps in glycolysis was more complicated than originally thought. The intermediate first gained energy as it was oxidized; only thereafter did it provide the energy for adding phosphate to ADP, yielding ATP. This led E. C. (Bill) Slater (1953) to revise Lipmann's proposed scheme for ATP formation coupled to the electron transport chain. He proposed that an additional compound, C, first formed a high-energy bond with A. The energy from that bond then facilitated the uptake of phosphate into ATP:

$$\begin{array}{c} AH_2 + B + C \rightleftharpoons A \sim C + BH_2 \\ \underline{A \sim C + ADP + P_i \rightleftharpoons A + C \pm ATP} \\ AH_2 + B + ADP + P_i \rightleftharpoons A + BH_2 + ATP. \end{array}$$

This version of the scheme set the agenda for many biochemists for the next twenty years – the race was on to identify C, the hypothesized intermediate. The search turned out to be futile, though, as no such intermediate exists.[5]

[5] Douglas Allchin has offered a detailed account of the quest for the nonexistent intermediate as well as lessons learned (1996; 1997). More recently he developed the idea that, although the search for a chemical intermediate could not succeed, other important results came out of the attempt. In particular, Allchin (2002) analyzed how Paul Boyer's research led to a number of discoveries, such as phosphohistidine, which figured as an intermediate not in oxidative phosphorylation, as

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